REMARKS

As presently claimed, the invention encompasses pharmaceutical compositions which comprises as an active ingredient a recombinant polyclonal antibody or a mixture of different monoclonal antibodies capable of reacting with or binding to an allergen. Claims 1 and 5-14 were examined in this case. Claims 10-12 were objected to for depending on canceled claim 2. The Examiner further objected to the abstract of the disclosure for exceeding the range of 150 words. Claims 1 and 5-14 were rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement and written description. Claims 1, 5, 9-12 were further rejected under 35 U.S.C. § 102(b) for being anticipated by U.S. Patent 5,789,208. Claims 1, 6-8, and 13-14 were rejected under 35 U.S.C. § 103(a) for obviousness over U.S. Patent 5,789,208 in view of U.S. Patent 5,670,626 and in further view of WO 96/09085. These objections and rejections are addressed below, in the order in which they appear in the Office Action.

Support for Amendments

Support for the amendments to claim 1, and to new claims 35-49, is found throughout the specification. Specifically, support for amended claim 1 can be found on page 3, lines 14-15 and page 6, lines 24-26. Claim 10 has been amended to eliminate reference to canceled claim 2. Support for new claims 35-38, can be found on page 1, line 22 through to page 2, line 25, and on page 9, lines 30-32; for claim 39 on page 16, lines 26-30; for claims 40 and 41, on page 5, lines 29-33; for claim 42 on page 6, lines 31-35; for claim 43 on page 8, lines 11-14; for claim 44 on page 10, lines 25-26; for claim 45 on page 15, lines 20-30; for claims 46 and 47 on page 12, lines 9-12; for claim 48 on page 17, lines 1-4; and for claim 49 on page 21, lines 1-2. No new matter is introduced.

A "marked up" version of the claims showing the changes made and an appendix of the claims as pending are attached.

Objections

Claims 10-12 were objected to for being dependent on canceled claim 2. Applicants have amended claim 10 to eliminate reference to canceled claim 2. Accordingly, this objection may now be withdrawn.

The Examiner has objected to the abstract of the disclosure for exceeding the word range of 150 words. Applicants have amended the abstract to now comply within the acceptable range. This objection may now be withdrawn.

Rejections Under 35 U.S.C. § 112, first paragraph

Claims 1 and 5-14 were rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement and written description.

The Examiner's central argument for lack of enablement is that monomeric immunoglobulin isotypes are incapable of crossing mucosal surfaces. Only polymeric IgA and IgM, can be transported across mucosal surfaces due to the presence of the J chain, which are lacking in other immunoglobulin isotypes. Applicants respectfully disagree.

Applicants assert that antibodies, regardless of isotype, need not be transported across mucosal surfaces for therapeutic benefit. In support of this assertion, Applicants enclose herewith the Declaration from John S. Haurum, Ph.D., M.D., a co-inventor in the present application. Therapeutic benefit from polyclonal antibody treatment for allergies may be provided in at least two ways: (i) at the mucosal surface, where polyclonal antibody recognition and binding of an allergen would prevent entry of the allergen into the circulatory system and where the entrapped allergen-immune complexes can subsequently be cleared; and (b) antibodies absorbed into the systemic blood circulation would recognize and bind allergens, and consequently, block binding sites on the allergen, thereby prevent recognition, binding, or response by the host immune system.

Moreover, the Examiner is directed to the cited reference in the above-mentioned Declaration. Dickinson et al. (J. Clin. Invest. 104:903-911, 1999) disclose that IgG

transport across mucosal surfaces do indeed occur. Transport is dependent on FcRn, which is analogous to sIgR and responsible for IgA or IgM transcytosis. FcRn specifically recognizes IgG isotypes and facilitates bi-directional transport across epithelial cells.

Thus, contrary to Examiner's assertion, antibodies do not absolutely require the J chain for efficient transport of immunoglobulins across mucosal surfaces. However, even if antibodies do not get transported across mucosal surfaces, therapeutic benefit is maintained, or even enhanced, since allergens are bound and cleared at the mucosal surface. Accordingly, this rejection may now be withdrawn.

The Examiner has also rejected claims 1 and 5-14 for lack of written description. While the Examiner concedes that Applicants are in possession of a pharmaceutical composition comprising recombinant polyclonal IgM and IgA immunoglobulin isotypes, the Examiner asserts that Applicants are not in possession of any other immunoglobulin isotypes. Applicants respectfully traverse this rejection.

Applicants first submit that the specification is replete with descriptions and methods for producing recombinant polyclonal antibodies. A description of the physical structure and properties of antibodies, including IgA, IgD, IgE, IgG, and IgM immunoglobulin isotypes, can be found on page 1 of the specification, line 22 through page 2, line 25. Applicants further argue that being in possession of a pharmaceutical composition comprising recombinant polyclonal IgA and IgM immunoglobulin isotypes, should also hold for all other immunoglobulin isotypes. If one can distinguish, describe, or produce an IgA or IgM molecule from all other immunoglobulin isotypes, then the converse should also be true; i.e., recombinant polyclonal IgD, IgE, and IgG immunoglobulin isotypes can be distinguished, described, or produced from all other immunoglobulin isotypes. Accordingly, this rejection should now be withdrawn.

Rejections Under 35 U.S.C. § 102(b)

Claims 1, 5, and 9-12 stand rejected under 35 U.S.C. § 102(b) for being anticipated by U.S. Patent No. 5,789,208. The Examiner states the '208 patent teaches a pharmaceutical composition comprising recombinant polyclonal antibodies with a pharmaceutically acceptable carrier in solution, which may be disease-specific, patient-specific, or both. Applicants respectfully disagree and traverse this rejection.

While the '208 patent does teach methods for the production of recombinant polyclonal antibodies, the '208 patent, neither mentions, nor appreciates the use of recombinant polyclonal antibodies for the treatment of allergies. The '208 patent discloses compositions of recombinant polyclonal antibodies, which recognize and bind to tumor antigens or infectious agents, and not to allergens. Furthermore, Examiner's reference to column 13, lines 61-67 of the '208 patent is unjustified. This passage of the aforementioned patent simply discloses that the methods of this patent can result in the production of recombinant antibodies, with no inference to antibodies that bind to allergens.

In an effort to expedite prosecution, however, Applicants have amended independent claim 1, to now recite a pharmaceutical composition comprising a recombinant polyclonal antibody which recognizes and binds to an allergen which has been inhaled, ingested, or is airborne. Claim 1 and claims dependent therefrom, are now such that rejection has been overcome by amendment, and may now be withdrawn.

Rejections Under 35 U.S.C. § 103 (a)

Claims 1, 6-8, and 13-14 stand rejected under 35 U.S.C. § 103 (a) for being obvious over U.S. Patent No. 5,789,208 in view of U.S. Patent No. 5,670,626, and in further view of WO 96/09085. The Examiner asserts that the '208 patent teaches advantages of recombinant polyclonal antibodies over monoclonal antibodies due to larger production scale as well as being directed to many different antigenic determinants. The '626 patent teaches pharmaceutical preparations containing human

monoclonal IgA antibodies specific for major allergenic proteins. The Examiner argues that the combination of the '208 and '626 patents renders the present invention obvious. Applicants respectfully disagree.

Applicants assert the Examiner has failed to establish a *prima facie* case of obviousness because there was no motivation to combine the aforementioned references. M.P.E.P. § 2143.01 states:

> "Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." (citations omitted)

There is no explicit or implicit motivation to combine the two references. Neither reference suggests nor contemplates recombinant polyclonal antibodies specifically formulated for the treatment of allergies, as now clearly claimed. The production of polyclonal antibodies in the '208 patent was envisaged for the treatment of neoplastic disorders and infectious diseases. The polyclonal antibodies described in the '208 patent are generated by and directed to tumor cells or parasite antigens, which are considerably more complex than allergens, in that the polyclonal antibodies are in reality, directed to whole tumor cells or parasites.

The '208 Patent

Of central importance to the '208 patent is the understanding that activation of the immune system plays a pivotal role in the therapeutic efficacy of the antibodies described in the '208 patent. Antibody detection of a targeted tumor cell/parasite requires or involves the activation of cell-mediated immunity, the complement pathway, the

inflammatory pathway, and phagocytes to promote clearance, as stated in the aforementioned Declaration of Dr. John S. Haurum. While extensive activation of these pathways is important for ridding the body of cancerous cells or infectious agents, such activation would be deleterious in treating allergies. For example, activating the inflammatory pathway as a consequence of cytotoxic T cell activation would result in anaphylaxis, due to the generation of the complement components, C3a and C5a and would thus be counter-productive as an allergy treatment. Clearly, one skilled in the art would have no motivation to associate a therapeutic strategy for the stimulation of the immune system with the treatment for allergies.

The '626 Patent

The '626 patent teaches only the use of a monoclonal antibody for treating IgE-mediated allergies. Treatment of allergies is effected through binding at a single antigenic determinant on the allergen with a monoclonal antibody at the mucosal surface, thereby preventing the allergen from being absorbed (Column 7, lines 34-50). However, a fundamental problem that is not contemplated by this approach is that an IgE-mediated allergenic response may still be elicited because, irrespective of whether an allergen traverses the mucus membrane, a single monoclonal antibody will not block all accessible epitopes resident on an allergen. Since each allergen contains numerous epitopes, it is more than likely that other epitopes on the allergen will still be exposed for recognition by IgE in the mucosal membranes. In this respect, polyclonal antibodies are far superior to monoclonal antibodies. Thus the '626 patent, in fact, teaches away from using polyclonal antibodies by narrowly focusing on the aggregation and clearance by a monoclonal antibody approach, while completely ignoring the need for a concomitant blocking of allergen-specific IgE accessibility to all allergenic epitopes of an allergy particle.

The present invention features polyclonal antibodies, regardless of isotypic class, for allergy treatment. The superiority of the present invention takes the following into

account: (i) polyclonal antibodies will recognize and bind to many antigenic determinants on an allergen, thereby rendering the allergen inaccessible to IgE detection, either through steric hindrance or by blocking epitope sites; (ii) multiple binding of polyclonal antibodies to an allergen will promote an immune complex to form a precipitin (monoclonal antibodies cannot form a precipitin unless the same antigenic determinant is expressed in multiple sites of the same allergen), which is easily cleared, as a mucus bolus, by peristalsis, or phagocytosed, if formed in the circulation; (iii) therapeutic benefit results, regardless of allergen or polyclonal antibodies being transported into the circulation (i.e., the present invention is both a prophylactic and therapeutic treatment for allergies). This dual therapeutic benefit is neither taught nor appreciated by either of the '208 or '626 patents.

Moreover, the Examiner's assertion that one of ordinary skill in the art would have been motivated to substitute the pharmaceutical composition comprising a human recombinant monoclonal antibody taught by the '626 patent for the recombinant polyclonal antibodies taught by the '208 patent is in error. The '626 patent, in fact, teaches away from using polyclonal antibodies because the abundance of proteases resident in the mucosal tissue would effect proteolysis of non-IgA immunoglobulins, Thus, IgA was specifically selected in the '626 patent due to its resistance to proteolytic cleavage.

Furthermore, the combined references do not teach or suggest all the claim limitations as the amended claims now read. Specifically, amended independent claim 1 now recites a recombinant polyclonal antibody, which is capable of reacting with epitopes derived from inhaled, ingested, or airborne allergens. Neither reference considers a recombinant polyclonal antibody which is capable of binding or reacting to ingested epitopes, nor do the combined references teach the topical administration of recombinant polyclonal antibodies to the urogenital mucosa, as described in claim 7.

Clearly, one skilled in the art would have no motivation, implicitly or explicitly, to combine the '208 and '626 patents to derive at the present invention.

WO 96/09085

Finally, the Examiner has rejected claim 9 for obviousness over the '208 patent in view of WO 96/09085. The '208 patent has been discussed supra. The WO 96/09085 document teaches a method for aerosolizing a powdered medicament. The Examiner states that it would have been obvious for one skilled in the art to substitute the powdered medicament, taught in WO 96/09085, for the polyclonal antibodies taught by the '208 patent. Applicants disagree.

Neither the '208 nor WO 96/09085 documents refer to recombinant polyclonal antibodies capable of reacting or binding to allergens. The WO 96/09085 document teaches only that dry powder medicaments can be produced for dispersing proteins, polypeptides and other drugs (page 3, lines 19-21). The '208 patent refers only to recombinant polyclonal antibodies for treating neoplasms and infectious agents. Thus, there is no impetus to combine these two references. Additionally, neither reference suggests or teaches the use of microspheres in a pharmaceutical composition. Accordingly, this rejection may be withdrawn.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is requested. Enclosed is a check in the amount of $26.00 for payment of the two additional dependent claims. If there are any other charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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ABSTRACT

A pharmaceutical composition for treating allergy is described. The composition comprises as an active ingredient a recombinant polyclonal antibody or a mixture of different monoclonal antibodies capable of reacting with or binding to an allergen together with one or more pharmaceutically acceptable excipients. The composition may be used topically as a solution, dispersion, powder, or in the form of microspheres. The polyclonal antibody is preferably a recombinant polyclonal antibody produced by phage display technology. The pairing of specific immunoglobulin variable region light chain and heavy chain maintained from the original polyclonal immune response or selected by panning using the allergen in question is preferably maintained by bulk transfer of the pairs into an expression vector. [The allergen may be an allergen of house dust mites, e.g. *Dermatophagoides farinae* or *D. pteronyssimus;* dander from cat, dog or horse; tree pollen, e.g. pollen from birch *(Betula alba),* alder, hazel, oak, willow, plane, beech, elm, maple, ash and hornbeam; grass pollen, e.g. pollen from timothy grass *(Phleum pratense),* bluegrass *(Poa pratense),* rye grass *(Lolium perenne),* Orchard grass *(Dactylis glomerata),* ragweed *(Ambrosia artemisiifolia),* sweet vernal grass *(anthoxanthum odoratum),* and rye *(Secale cereale);* or fungi (e.g. *Alternaria, Aspergillus, Cladosporium* and *Penicillium)*].

Claims

1. (Amended) A pharmaceutical composition comprising as an active ingredient a recombinant polyclonal antibody capable of reacting with or binding to proteins or epitopes derived from an inhaled, ingested, or airborne [an] allergen, together with one or more [pharmaceutical] pharmaceutically acceptable excipients.

10. (Amended) A pharmaceutical composition according to claim [2] 1, wherein the recombinant polyclonal antibody is generated by phage display technology.

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Claims as Pending

1. (Amended) A pharmaceutical composition comprising as an active ingredient a recombinant polyclonal antibody capable of reacting with or binding to proteins or epitopes derived from an inhaled, ingested, or airborne allergen, together with one or more pharmaceutically acceptable excipients.

5. A pharmaceutical composition according to claim 1, which composition is free of the allergen to which the antibody is reactive or binds.

6. A pharmaceutical composition according to claim 1, comprising at least one pharmaceutically acceptable excipient capable of effecting topical application of said recombinant polyclonal antibody.

7. A pharmaceutical composition according to claim 5, which is intended for topical administration to the oropharynx, nasal cavity, respiratory tract, gastrointestinal tract, conjunctival mucosa, vagina, urogenital mucosa, or for dermal application.

8. A pharmaceutical composition according to claim 7, wherein the respiratory tract is selected from nasal, oral, pharyngeal, bronchial, or alveolar mucosa.

9. A pharmaceutical composition according to claim 1, which is provided as a solution, dispersion, powder or in the form of microspheres.

10. (Amended) A pharmaceutical composition according to claim 1, wherein the recombinant polyclonal antibody is generated by phage display technology.

11. A pharmaceutical composition according to claim 10, wherein the recombinant polyclonal antibody is generated under such conditions that the immunoglobulin heavy chain variable region and light chain variable region gene segments are linked together in a parental library in order to allow for the bulk transfer of variable region light chain and heavy chain gene pairs from one vector to another, while allowing stable pairing of specific immunoglobulin variable region light chain and heavy chain gene segments as they are present upon selection from the parental library of immunoglobulin variable region light chain and heavy chain gene segment pairs encoding antibody molecules capable of reacting with or binding to an allergen.

12. A pharmaceutical composition according to claim 10, wherein the recombinant polyclonal antibody is generated under such conditions that the immunoglobulin heavy chain variable region and light chain variable region gene segments are linked together in order to allow for the bulk transfer of specific variable region light chain and heavy chain gene pairs from one vector to another, while allowing

stable pairing of specific immunoglobulin variable region light chain and heavy chain gene segments as they are present in the original polyclonal immune response of an animal or human individual.

13. A pharmaceutical composition according to claim 1, wherein the allergen is an allergen of house dust mites, dander from cat, dander from dog, dander from horse, tree pollen, grass pollen, or fungi.

14. A pharmaceutical composition according to claim 1, comprising the recombinant polyclonal antibody in an amount in the range of 1μg to 1g per unit dosage form.

35. (New) A pharmaceutical composition according to claim 1, wherein said polyclonal antibody is an IgG antibody.

36. (New) A pharmaceutical composition according to claim 1, wherein said polyclonal antibody is an IgM antibody.

37. (New) A pharmaceutical composition according to claim 1, wherein said polyclonal antibody is an IgA antibody.

38. (New) A pharmaceutical composition according to claim 1, wherein said polyclonal antibody is an IgD antibody.

39. (New) A pharmaceutical composition according to claim 1, wherein said polyclonal antibody has antibody molecules from a mixture of antibody classes.

40. (New) A pharmaceutical composition according to claim 1, wherein said polyclonal antibody binds said allergen with sufficient density to mediate the elimination of said allergen from a patient.

41. (New) A pharmaceutical composition according to claim 1, wherein said polyclonal antibody binds said allergen with a higher antibody density than a monoclonal antibody.

42. (New) A pharmaceutical composition according to claim 1, wherein said polyclonal antibody does not cross-react with endogenous self-antigens in a patient.

43. (New) A pharmaceutical composition according to claim 1, wherein said polyclonal antibody does not elicit an anaphylactic response in humans.

44. (New) A pharmaceutical composition according to claim 1, wherein said polyclonal antibody is a fully human antibody.

45. (New) A pharmaceutical composition according to claim 1, wherein the variable region of said polyclonal antibody has a mutation.

46. (New) A pharmaceutical composition according to claim 1, wherein at least 85% of the antibody molecules in said composition are target-specific.

47. (New) A pharmaceutical composition according to claim 1, wherein at least 90% of the antibody molecules in said composition are target-specific.

48. (New) A pharmaceutical composition according to claim 1, wherein said polyclonal antibody is a complete antibody molecule or fragment thereof such as an F_{ab} fragment.

49. (New) A pharmaceutical composition according to any of claim 1, wherein said composition is provided as a microsphere, liposome, polyethylene glycol-conjugated complex, or complex of positively or negatively charged excipients with antibody molecules of the opposite charge, wherein said composition prolongs the clearance of said polyclonal antibody in a patient.